

AD \_\_\_\_\_

AWARD NUMBER: W81XWH-08-1-0556

TITLE: Feasibility Study of a Novel Diet-Based Intervention for Prostate Cancer

PRINCIPAL INVESTIGATOR: J. Kellogg Parsons, M.D.

CONTRACTING ORGANIZATION: University of California, San Diego  
La Jolla, CA 92093

REPORT DATE: September 2009

TYPE OF REPORT: Annual Summary

PREPARED FOR: U.S. Army Medical Research and Materiel Command  
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;  
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

# REPORT DOCUMENTATION PAGE

Form Approved  
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.

1. REPORT DATE 1 September 2009	2. REPORT TYPE Annual Summary	3. DATES COVERED 1 Sep 2008 – 31 Aug 2009		
4. TITLE AND SUBTITLE  Feasibility Study of a Novel Diet-Based Intervention for Prostate Cancer		5a. CONTRACT NUMBER		
		5b. GRANT NUMBER W81XWH-08-1-0556		
		5c. PROGRAM ELEMENT NUMBER		
6. AUTHOR(S)  J. Kellogg Parsons, M.D.  E-Mail: jkparsons@ucsd.edu		5d. PROJECT NUMBER		
		5e. TASK NUMBER		
		5f. WORK UNIT NUMBER		
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)  University of California, San Diego La Jolla, CA 92093		8. PERFORMING ORGANIZATION REPORT NUMBER		
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012		10. SPONSOR/MONITOR'S ACRONYM(S)		
		11. SPONSOR/MONITOR'S REPORT NUMBER(S)		
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited				
13. SUPPLEMENTARY NOTES				
14. ABSTRACT Our goal is to develop a practical, diet-based intervention for prostate cancer. We plan to implement a randomized clinical trial of a novel dietary intervention that utilizes a central, telephone-based counseling program to promote vegetable intake among prostate cancer patients who are being treated with active surveillance. As part of this trial, we will test whether a gene fusion biomarker will predict disease progression in this patient population. During the first year of the funding period, I accomplished five major tasks. First, I several key organizational components of the trial, including a) writing of the study protocol; b) development of the infrastructure for executing the telephone-based dietary intervention, including personnel and printed materials; c) development of the infrastructure for performing dietary assays, including obtainment of a fluoroscopic detector for measuring dietary biomarkers; d) establishment of the protocols for obtaining and processing patient specimens, including those to be submitted for TMPRSS2:ERG gene fusion analysis; and e) obtainment of IRB approval from UCSD. Second, I published two peer-reviewed manuscripts. Third, I extended my participation in the Cancer and Leukemia Group B cooperative study group. Fourth, through increased participation in CALGB, I expanded the scope of the trial to include twice as many prostate cancer patients as originally conceived. Finally, I helped secure additional funding for performing the trial, including a NCI RO-1 grant. I anticipate that, at the beginning of the second year of the funding period, the trial will open for accrual and testing of the dietary intervention will begin.				
15. SUBJECT TERMS prostate cancer, diet, watchful waiting, active surveillance				
16. SECURITY CLASSIFICATION OF:  a. REPORT U		17. LIMITATION OF ABSTRACT UU	18. NUMBER OF PAGES 68	19a. NAME OF RESPONSIBLE PERSON USAMRMC
b. ABSTRACT U				19b. TELEPHONE NUMBER (include area code)
c. THIS PAGE U				

## **Table of Contents**

	<u>Page</u>
<b>Introduction.....</b>	<b>1</b>
<b>Body.....</b>	<b>2</b>
<b>Key Research Accomplishments.....</b>	<b>4</b>
<b>Reportable Outcomes.....</b>	<b>5</b>
<b>Conclusion.....</b>	<b>6</b>
<b>References.....</b>	<b>7</b>
<b>Appendices.....</b>	<b>8</b>

## I. Introduction

Despite substantial advances in early detection and treatment, prostate cancer remains the most commonly diagnosed non-cutaneous cancer and the second leading cause of cancer death among U.S. men. The enormous scope of this public health problem calls for the development of innovative approaches to prostate cancer prevention, control, and treatment.

One potential novel approach is dietary modification. Epidemiological and pre-clinical studies suggest that alterations in nutritional intake may protect against prostate cancer initiation and progression. However, despite widespread public interest in this topic, there are very few clinical studies investigating the potential benefits of diet-based interventions for prostate cancer.

We have successfully developed and pilot tested a telephone-based dietary intervention for prostate cancer patients based on well-established principles of social cognitive theory.<sup>1,2</sup> This relatively straightforward, low-cost intervention—which increases vegetable intake and decreases fat intake—is the first to utilize diet as a form of primary clinical therapy for prostate cancer. Due to its practicality, simplicity, and proven benefits to cardiovascular and overall health, this intervention would be widely applicable. Use in an active surveillance (“watchful waiting”) population may potentially spare thousands of patients each year from the considerable side effects of surgery and radiation.

*We hypothesize that a vegetable-intense diet will decrease disease progression and anxiety in men with prostate cancer.* Our goal is to develop a practical, diet-based intervention for prostate cancer. We plan to implement a randomized clinical trial of a novel dietary intervention that utilizes a central, telephone-based counseling program to promote vegetable intake among prostate cancer patients who are being treated with active surveillance. As part of this trial, we will test whether a gene fusion biomarker will predict disease progression in this patient population.

## **II. Body**

### **Progress to Date**

During the first year of the funding period, I have made substantial progress in 5 specific areas.

#### *1. Organizational components for Initiating the Randomized Trial*

I completed five key organizational components of study at the University of California San Diego (UCSD) Moores Comprehensive Cancer Center, all of which are necessary for implementing the trial: a) I wrote the study protocol; b) I oversaw development of the infrastructure for executing the telephone-based dietary intervention, including personnel and printed materials; c) I oversaw development of the infrastructure for performing dietary assays, including obtainment of a fluoroscopic detector for measuring dietary biomarkers; d) I established the protocols for obtaining and processing patient specimens, including those to be submitted for TMPRSS2:ERG gene fusion analysis; and e) I secured local IRB approval from UCSD. In addition, I completed and submitted the initial application materials for human subjects research protection to the DOD.

#### *2. Publications*

Based on additional analyses of the pilot data for the current study, I published one peer-reviewed manuscript.<sup>3</sup> In addition, I published a second peer-reviewed manuscript focusing on the complex background data related to the trial.<sup>4</sup>

#### *3. Expanded participation in Cancer and Leukemia Group B (CALGB)*

Because the pilot study for this trial was funded by the Cancer and Leukemia Group B (CALGB), members of the CALGB leadership have taken an active interest in its development. As a result, I substantially expanded my participation in the CALGB organizational structure. Last year, I joined the CALGB Prevention Sub-committee, adding to my role as a standing member of the Genitourinary Surgery Sub-committee and Genitourinary Committee. I attended two CALGB group meetings (in November 2008 and June 2009) at which I made presentations to the GU Surgery and Prevention Sub-committees and GU Committee regarding the status of the trial. I also supplied regular updates to members of the CALGB leadership through e-mail correspondence, participated in conference calls, and broadened my contacts with other clinician scientists in the CALGB network.

#### *4. Expansion of the current study*

My increased participation in CALGB presented me the tremendous opportunity to expand the scope of the trial from the two sites—UCSD and Roswell Park Cancer Institute—originally detailed in the Statement of Work when members of the CALGB leadership suggested that it be run as a multi-center national trial utilizing the CALGB infrastructure.

Therefore, in collaboration with Dr. James Marshall of Roswell Park, I reworked the initial power calculations as follows: assuming a drop-out rate of 5%, to observe a reduction from 30% to 15% in the probability that patients progress with 90% power at a

level of 0.05 will require 200 men randomized to each of the two study groups, for a total of 400 randomized participants; for the same number of participants, we will have 80% power to observe a reduction in progression from 30% to 20%.

### ***5. Funding***

With the support of the GU Surgery and Prevention Sub-committees and the CALGB leadership, I helped develop and submit an expanded protocol—based extensively on the protocol outlined in the Statement of Work—as an RO-1 application to the National Cancer Institute to fund the expanded study CALGB. The primary outcome variables and dietary intervention of this expanded study are identical to those listed in the Statement of Work. Dr. James Marshall of Roswell Park is the Principal Investigator and Dr. Marshall and I are study Co-chairs. As Protocol Chair, I share the ultimate responsibility for the orderly and scientific conduct of all research activities associated with the trial.

The RO-1 application received an initial priority score of 196. We responded to the reviewer's comments and resubmitted; the resubmission priority score was 162. During Q1 2008-2009, we again responded to the reviewers and resubmitted. During Q2 2008-2009, the 2<sup>nd</sup> resubmission priority score was 155, corresponding to the 14<sup>th</sup> percentile. NCI officials then requested additional responses to reviewers prior to making a final decision on funding status. During Q3 2008-2009, I drafted additional, detailed responses to the reviewers which Dr. Marshall and I then submitted for review. During Q4 2008-2009, we received word that we had received a 5-year, RO-1 award. Since that time, I have been working with Dr. Marshall to revise the CALGB protocol, finalize IRB status, and open the study to accrual.

In addition, in Q1 2008-2009, I received a grant from the Hope for a Cure Foundation to purchase a fluoroscopy detector necessary for performing dietary biomarker studies for the trial.

### **Problem areas**

*There are no current problems impeding performance of the trial.* As stipulated in the approved Statement of Work, the original grant timeline—which included a 6 month period to account for potential funding and regulatory issues—estimated that the trial would open to accrual in March 2009. With the additional time required to secure the RO-1 funding, we are now anticipating a start date in November 2009. The revised timeline will depend upon the exact start date and will be submitted at the end of the next annual reporting period.

### **Work to be performed during next reporting period**

As noted above, I anticipate that the trial will begin in November 2009. Following this, we will accrue patients to study and implement testing of the intervention.

### **III. Key Research Accomplishments**

- Completion of 5 key organizational components for the trial:
  - Writing of the study protocol.
  - Development of the telephone-based dietary intervention infrastructure.
  - Development of the dietary assay infrastructure.
  - Establishment of the protocol for obtaining and processing patient specimens at UCSD.
  - Obtainment of UCSD IRB approval.
- Publications
  - Two peer-reviewed papers related to the study.
- Expanded participation in Cancer and Leukemia Group B (CALGB)
  - CALGB Prevention and GU Sub-Committees and GU Committee.
  - Presentations at two CALGB group meetings.
  - Regular conference calls and email correspondence.
- Funding
  - National Cancer Institute RO-1
  - Hope for a Cure Foundation

#### **IV. Reportable Outcomes**

##### Peer reviewed manuscripts.

Silberstein J and **Parsons JK**. Current concepts in diet and prostate cancer. Aging Health, 4: 495-50, 2008.

**Parsons JK**, Newman V, Mohler JL, Pierce JP, Flatt S, Messer K, and Marshall J. Dietary intervention after definitive therapy for localized prostate cancer: results from a pilot study. Can J Urol, 16(3):4648-4654, 2009.

##### Funding

- National Cancer Institute 5R01 CA1329510182
  - “A randomized, multicenter, phase 3 trial of a dietary intervention for prostate cancer patients treated with active surveillance.”
  - 
  - PI: Marshall
  - Role: Study Co-chair and co-investigator
- Hope for a Cure Foundation (San Diego, CA)
  - toward the purchase of a fluoroscopic detector for biomarker assays, to be housed in the UCSD Moores Cancer Center Shared Nutrition Resource

## **V. Conclusion**

In summary, I have achieved substantial progress during the first year of the funding period. I have completed several key organizational tasks for implementing the randomized clinical trial, published two peer reviewed manuscripts, expanded the scope of the trial by extending my participation in the CALGB cooperative group, and secured additional funding for performing the trial.

I anticipate that, during the second year of the funding period, the trial will open for accrual and testing of the dietary intervention will begin.

#### **IV. References**

1. Parsons JK, Newman V, Mohler JL, Pierce JP, Flatt S, and Marshall J. Dietary modification in prostate cancer patients on active surveillance: a randomized, multi-center feasibility study. *BJU Int*, 101: 1227-1231, 2008.
2. Parsons JK, Newman V, Mohler J, Pierce JP, Paskett E, and Marshall J. The Men's Eating and Living (MEAL) Study: A Cancer and Leukemia Group B pilot trial of dietary intervention for the treatment of prostate cancer. *Urology*, 72: 633-7, 2008.
3. Silberstein J and Parsons JK. Current concepts in diet and prostate cancer. *Aging Health*, 4: 495-50, 2008.
4. Parsons JK, Newman V, Mohler JL, Pierce JP, Flatt S, Messer K, and Marshall J. Dietary intervention after definitive therapy for localized prostate cancer: results from a pilot study. *Can J Urol*, 16(3):4648-4654, 2009.

## **IV. Appendices**

### **Copies of Peer Reviewed Manuscripts**

#### **Current Concepts in Diet and Prostate Cancer**

Jonathan Silberstein M.D.<sup>1</sup> and J. Kellogg Parsons, M.D., M.H.S.<sup>1-3</sup>

<sup>1</sup>Division of Urologic Oncology, Department of Surgery, University of California, San Diego Medical Center

<sup>2</sup>Moores UCSD Comprehensive Cancer Center

<sup>3</sup>Veterans Affairs Medical Center, San Diego, CA

Correspondence: Jonathan Silberstein, M.D.

Division of Urology  
UCSD Medical Center  
200 West Arbor Drive #8897  
San Diego, CA 92103-8897  
Tel: 619-543-2659  
Fax: 619-543-6573  
E-mail: [jsilberstein@ucsd.edu](mailto:jsilberstein@ucsd.edu)

Key words: diet, prostate cancer, lycopene, soy, cruciferous vegetables, vitamin E, and selenium, vitamin D, calcium, zinc, meat, pomegranate, green tea, β-carotene

Running title: Diet and Prostate Cancer

## **Summary**

Increasing evidence suggests that diet influences the initiation and progression of prostate cancer. Herein, we review associations of specific foods and nutrients with prostate cancer, summarizing important and clinically relevant emerging data on this complex topic. Foods and nutrients associated with decreased risk of prostate cancer include lycopene, soy, cruciferous vegetables, vitamin E, and selenium. Although prospective clinical trials of dietary supplements and dietary modification to prevent or control prostate cancer are underway, definitive clinical evidence is currently lacking.

## **Introduction**

Prostate cancer is the most commonly diagnosed noncutaneous cancer and the second leading cause of cancer death among United States men. In 2007 in the United States, 218,890 men were diagnosed with, and 27,050 men died of, prostate cancer (American Cancer Society, Cancer Facts and Figures, at [www.cancer.org](http://www.cancer.org)). Globally, prostate cancer incidence is on the rise.[1] In the U.S.A., the cost of treating prostate cancer in 2003 was estimated to be more than 4 billion dollars annually.[2] The magnitude of this public health problem calls for the development of novel approaches to prostate cancer prevention and control.

Accumulating epidemiological and pre-clinical evidence suggests that diet may substantially alter prostate cancer initiation and progression. Associations of specific dietary constituents with prostate cancer risk would intimate that modulation of diet is a potential therapy for prostate cancer prevention and control. In this review, we identify foods and nutrients potentially associated with prostate cancer risk and outline ongoing clinical trials of dietary supplements and modification to prevent or control prostate cancer.

## **Lycopene (Tomato)**

Lycopene is an antioxidant commonly found in tomatoes, watermelon, and pink grapefruit.[3] Lycopene is a free radical scavenger and has been shown to reduce the amount of oxidative DNA damage in cell culture and animal studies.[4]

Epidemiological data has been inconsistent. The Health Professionals Follow Up Study (HPFS), a prospective epidemiological based study based on mailed dietary

questionnaires noted a significantly reduced risk of prostate cancer in those who consume higher quantities of tomato products. [5-7] However, the Prostate, Lung, Colorectal and Ovarian Screening Trial (PLCO) a multi-center cancer screening trial in which patients completed a 137 item food frequency questionnaire at baseline did not demonstrate a significant reduced risk with lycopene or tomato product consumption.[8]

Still, broader analyses of published data suggest a slight protective effect for tomatoes. A critical review performed by the U.S. Food and Drug Association observed a decreased risk of prostate cancer with higher tomato intake but no significant association of lycopene with prostate cancer.[9] Finally, in a meta-analysis of 21 published studies, Etminan and colleagues observed that participants with the highest intake (fifth quintile of intake) of raw tomatoes [Relative Risk (RR) 0.89, 95% CI 0.8 to 1.0] or cooked tomatoes (RR 0.81 95% CI 0.71 to 0.92) had a modest reduction in prostate cancer risk.[10] These investigators furthermore noted that while lycopene consumption was not associated with prostate cancer risk (RR 0.99, 95% CI 0.93-1.06), higher serum lycopene concentrations were associated with decreased risk (RR 0.85, 95% CI 0.75-0.97).

Interest in the potential therapeutic benefits of lycopene and/or tomatoes has lead to a small number of clinical trials that have produced promising—yet preliminary—results. Stacewicz-Sapuntzakis and Bowen placed thirty-two patients with prostate cancer on a tomato paste-rich diet 3 weeks before their scheduled prostatectomy. The patients consumed 26.8 mg of lycopene per day, compared with their usual mean intake of 5 mg/day. These investigators noted significant reductions in serum PSA concentrations and increases in apoptotic index in the intervention group compared with

the controls.[11] Similarly, Kucuk and colleagues randomized 26 patients with newly diagnosed prostate cancer to receive tomato oleoresin extract containing 30 mg of lycopene or no supplementation for 3 weeks before radical prostatectomy. When compared with controls, the intervention group was found to have smaller tumors, less involvement of surgical margins, and less diffuse involvement of the prostate by high-grade prostatic intraepithelial neoplasia.[12] Still, while interesting, clinically significant outcomes such as (prostate cancer incidence or survival) have yet to be examined.

## **Soy**

Soy is rich in isoflavones, most notably genistein and daidzein, and its consumption is greater in populations with lower incidence of prostate cancer. [13] While research is ongoing, isoflavonoids may mitigate prostate cancer risk through a variety of proposed mechanisms. Various investigators have demonstrated that soy may influence androgen receptor activity and the hormonal milieu.[13, 14] Additionally, genistein and daidzein have been demonstrated to have direct impact on cell cycle regulation and telomerase activity of prostate cancer cell lines.[15, 16]

Some but not all epidemiological studies have observed a decreased risk of prostate cancer with increased soy intake. In the Adventist Health Study, frequent consumption of soy, defined as more than once a day, was associated with a 70% reduction of prostate cancer risk (RR 0.30, 95% CI 0.1 to 1.0, *P*-value for linear trend = 0.03).[17] While data from other observational studies has been conflicting, in a meta-analysis of eight previously published studies, consumption of soy food was related to

an approximately 30% reduction in prostate cancer risk, strongly supporting its beneficial effects.[18]

In addition, several pilot clinical trials have noted reduction of prostate-specific antigen (PSA) levels in men with prostate cancer who are placed on high soy diets suggesting a potentially therapeutic role for high soy diets.[19-21] Schröder et al. performed a dietary-based intervention on 49 patients with a history of prostate cancer and rising PSA levels after radical prostatectomy or radiotherapy. In a randomized clinical trial, a dietary supplement consisting of soy, isoflavones, lycopene, silymarin and antioxidants was associated with a 2.6-fold increase in the PSA doubling time from 445 to 1150 days for the supplement and placebo periods, suggesting that the soy-based dietary supplement used in this study delayed PSA progression.[22] In another study of 41 patients with asymptomatic recurrent prostate cancer, a diet high in soy and tomatoes was associated with significantly increased serum lycopene levels and urinary isoflavone levels and decreased serum vascular endothelial growth factor and PSA.[23]

## **Cruciferous Vegetables**

Cruciferous vegetables include broccoli, broccoli sprouts, cauliflower, radishes, cabbage, brussels sprouts, kale, collard greens, and bok choy. These vegetables contain a number of nutrients and phytochemicals with health benefits and potential cancer chemopreventive properties, including folate, fiber, carotenoids and chlorophyll. Crucifers are rich sources of glucosinolates, substances which after consumption are hydrolyzed to biologically active compounds called indoles and isothiocyanates. In animal models, indole-3-carbinol has been shown to inhibit cell growth and induce

apoptosis in CaP cells.[24] Isothiocyanates induce expression of cytoprotective phase 2 enzymes in multiple prostate tumor cell lines,[25, 26] promote apoptosis of prostate cancer PC-3 cells in vitro, and inhibit growth of PC-3 xenografts in nude mice. [27] In the rat, oral ingestion of broccoli sprout extract containing isothiocyanates increases phase 2 enzyme activity in the prostate. [28] Interestingly, a recent study indicated that rats fed a combination tomato and broccoli diet had greater suppression of prostate tumors than rats fed either tomato or broccoli alone, suggesting a synergistic effect of the two dietary components.[29]

Epidemiologic studies have demonstrated conflicting results with respect to the association of prostate cancer and cruciferous vegetable intake. In the PLCO, risk of extraprostatic prostate cancer (stage III or IV tumors) decreased with increasing vegetable intake ( $RR = 0.41$ , 95% CI = 0.22 to 0.74, for high versus low intake;  $P_{trend} = 0.01$ ); this association was mainly explained by intake of cruciferous vegetables.[30] Although the HPFS demonstrated no significant overall association of baseline cruciferous vegetable intake and incident prostate cancer, restriction of the analyses to men who had undergone PSA testing to reduce the potential for detection bias, or to men with more consistent intake of vegetables over the 10 years before initiation of the study, showed significant inverse associations of crucifer intake with prostate cancer.[31] However, in the EPIC study, crucifers were not associated with prostate cancer risk.[32]

Based on these observations, a small number of randomized clinical trials have been performed to explore the potential for using vegetable-intense diets as a form of prostate cancer therapy. In a study by Ornish and colleagues, patients with less

aggressive prostate cancer on a program of active surveillance were randomized to either a control condition or an intensive lifestyle program that included a vegan diet supplemented with soy, fish oil, vitamin E, selenium and vitamin C, moderate aerobic exercise, stress management techniques, and participation in a 1-hour support group once weekly to enhance adherence to the intervention. PSA decreased by 4% in the experimental group but increased by 6% in the control group.[33] It is not clear what role cruciferous vegetable consumption played in PSA reduction. In another study of prostate cancer patients on active surveillance, these same investigators reported significant alterations in prostate gene expression patterns in response to comprehensive lifestyle changes, including a strict vegan diet.[34] In the Men's Eating and Living (MEAL) study, 74 men with prostate cancer were randomized to receive either telephone-based dietary counseling or standardized, written nutritional information. After 6 months of follow-up, mean daily intakes of total vegetables, crucifers, tomato products, and beans/legumes increased and fat intake decreased in the study group, while there were no significant changes in the control arm.[35] This study proved that simple telephone based counseling can have a significant impact on patient's diets and this may be a means of performing reliable dietary based interventions for patients with prostate cancer.

## **Vitamin E**

Vitamin E is a collective term for four tocopherols and four tocotrienols. The main dietary sources of vitamin E are vegetable oils.  $\alpha$ -tocopherol is thought to be the most

biologically active form and is the form found in dietary supplements.[36] Vitamin E may impact prostate cancer through its inhibition of NF-KappaB, a transcriptional factor linked to the development of prostate malignancy.[37] Additionally, vitamin E has been demonstrated to modulate cell cycle proliferation, and  $\alpha$ -tocopheryl succinate has been demonstrated to induce apoptosis in prostate cancer cell lines.[38, 39]

Vitamin E has generated a great deal of interest based on the results of the Alpha-Tocopherol, Beta-Carotene (ATBC) trial, which randomized 19,000 Finnish male smokers to vitamin E (50 mg), beta-carotene (20 mg), both, or placebo daily for 5 to 8 years (median, 6.1 years). The primary endpoint of the study was incident lung cancer; however, significant reductions in incident prostate cancer (32%) and prostate cancer deaths (41%) were noted.[40]

Although the HPFS and the PLCO observed no overall associations of prostate cancer risk and vitamin E consumption, both studies demonstrated in subset analyses a decreased risk of advanced or metastatic/fatal prostate cancer with vitamin E intake—but only among current and recent smokers.[41, 42] Similarly, the NIH-AARP Diet and Health Study noted an inverse association of dietary  $\gamma$ -tocopherol and risk of advanced prostate cancer only (for highest versus lowest quintile: RR, 0.68; 95% CI, 0.56-0.84;  $P_{\text{trend}} = 0.001$ ).[43]

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) is a large phase 3 randomized, placebo-controlled trial of selenium and vitamin E supplementation to determine if these compounds decrease the risk of prostate cancer. The study was opened in 2001 and finished accrual of nearly 35,000 participants in 2004. Participants are randomized to selenium alone (200  $\mu\text{g}/\text{day}$  from L-selenomethionine), vitamin E

alone (400 IU/day of all rac  $\alpha$ -tocopheryl acetate), both, or placebo for a minimum of 7 years. The study is anticipated to report results in 2013.[44]

## Selenium

Selenium is an essential trace nutrient that humans ingest through plant consumption. Selenium is believed to influence tumorigenesis through a variety of mechanisms, including androgen receptor signaling modulation, induction of apoptosis, and growth inhibition in prostate cancer cells.[45, 46]

The relationship between selenium and prostate cancer was serendipitously described in a randomized control trial of skin carcinomas in which 200  $\mu\text{g}$  of selenium daily significantly reduced incident prostate cancer (hazard ratio = 0.48, 95% CI = 0.28–0.80)[47, 48] Studies of In a meta-analysis of 16 studies (11 cohort and 5 case-control), Etminan and colleagues observed a pooled RR of prostate cancer for any intake of selenium of 0.72 (95% CI = 0.61–0.84) for cohort studies and 0.74 (0.61–1.39) for case-control studies. Similarly, the pooled RR of moderate selenium intake was 0.74 (0.61–0.90) for cohort studies and 0.74 (0.39–1.39) for case-control studies. These data suggest that selenium intake may reduce the risk of prostate cancer, and are notable in that they considered different methods of assessing selenium exposure, including food frequency questionnaires (which are potentially susceptible to recall bias), blood and plasma levels, and nail clippings.[49] The SELECT trial and a series of other smaller intervention based studies will further elucidate these associations.[50]

## Vitamin D

Vitamin D is technically a steroid hormone. It is produced in the skin in a reaction catalyzed by ultraviolet light and undergoes several hydroxylation reactions in the liver and kidney to its active metabolic forms. Vitamin D may decrease the risk of prostate cancer through its pro-apoptotic influence or its role as a nuclear transcription factor that regulates cell growth and differentiation.[51]

Risk of prostate cancer mortality increases with increased latitude from the equator.[52] Geographic distribution of prostate cancer mortality is the inverse of that of UV radiation. This effect is strongest in counties north of 40° N latitude, where vitamin D synthesis is limited to non-winter months.[53] Vieth and colleagues noted in a cohort of men on active surveillance that PSA progression was slower during the spring/summer than during the rest of the year.[54]

Despite these observations, there has been a lack of prospective epidemiologic data definitively linking prostate cancer risk with vitamin D use.[55-57] One reason may be that there are multiple factors that influence circulating 25(OH)D concentrations, including region as a surrogate of UV-B radiation exposure, behaviors related to sun exposure, skin pigmentation, BMI, season, and age.[58]

### **β-Carotene**

Carotene is an [orange photosynthetic pigment](#) important for [photosynthesis](#). There are several isoforms and β-carotene is the more common form and can be found in [yellow](#), [orange](#), and [green](#) leafy [fruits](#) and [vegetables](#). Generally, the greater the intensity of the orange color of the fruit or vegetable, the more β-carotene it contains. In

vivo experimentation has demonstrated that β-carotene may significantly reduce the growth of various prostate cancer cell lines.[59]

In the EPIC prospective observational study, higher plasma lycopene and total carotenoids were associated with a reduction in risk of advanced prostate cancer.[60] In the ATBC, for men taking β-carotene (20 mg/d for a median of 6 years) compared with placebo there was a modest but statistically nonsignificant increase in risk of prostate cancer.[61] In the Physicians' Health Study, supplemental β-carotene (50 mg on alternate days) was not associated with overall prostate cancer risk.[62] However, in a follow-up study, men with the lowest quartile of plasma β-carotene assigned at random to receive β-carotene supplementation had a significant reduction in prostate cancer risk (RR = 0.68, 95% CI, 0.46–0.99).[63]

### **Green Tea**

Green tea, which is made from an unfermented leaf extract of the plant *Camellia sinensis*. Green teas contain substances called catechins, including epigallocatechin (EGCG). EGCG has been demonstrated in vivo to suppress prostate tumor growth and tumor angiogenesis and to promote tumor apoptosis.[64, 65]

In a recent large prospective Japanese study, green tea consumption of 5 or more cups per day was associated with a decreased risk of advanced prostate cancer (RR 0.52, 95% CI: 0.28–0.96). There was no association with localized prostate cancer.[66]

### **Pomegranate Juice**

Pomegranate, a rich source of polyphenolic compounds called ellagitannins, has been reported to have higher antioxidant activity than red wine or green tea.[67] In vivo data suggests that pomegranate and ellagitannins may have antineoplastic potential through inhibition of angiogenesis and prostate cancer cell growth and modulation of androgen receptor pathways.[68] [69] Epidemiological evidence is lacking. However, Pantuck and colleagues demonstrated in a phase 2 study of men with rising PSA after surgery or radiation that pomegranate juice increased mean PSA doubling time from 15 months to 54 months.[70] Further investigations are ongoing.

## **Meat and Fat**

There are moderate but inconsistent epidemiologic associations of increased meat and fat consumption with elevated risk of prostate cancer.[71] [57] Hypotheses to explain these associations include exposure to carcinogenic pesticides, altered hormonal milieus, increased exposure to carcinogenic fatty acids, and increased production of reactive oxygen species which intercalate in DNA base pairs and result in mutations.[72]

In a systematic review of 33 epidemiologic studies, Fleshner and colleagues concluded that there is reasonable evidence that increased dietary fat intake is associated with an increased risk of prostate cancer.[73] In the Cancer Prevention Study II Nutrition Cohort, African American men with high consumption of cooked processed meats (sausages, bacon, and hot dogs) were more likely to be diagnosed with prostate cancer (RR, 2.7; 95% CI, 1.3–5.3 for highest versus lowest quartile;  $P(\text{trend}) = 0.008$ ).[74] Other recent studies, however, have not observed these

associations. In the large multi-institutional European Prospective Investigation into Cancer and Nutrition (EPIC), involving almost a hundred and fifty thousand men with mean follow-up of 8.7 years, there was no significant association between dietary fat (total, saturated, monounsaturated, and polyunsaturated fat and the ratio of polyunsaturated to saturated fat) and risk of prostate cancer.[75] Similarly in the Multiethnic Cohort Study, a prospective study of 87,000 multiethnic Americans the authors found no indication that intake of fat or meat substantially affects prostate cancer risk.[76]

Recent observational data intimate that weight loss and decreased fat intake may be beneficial. Among 69,991 men in the Cancer Prevention Study II Nutrition Cohort, weight loss >11 lbs over 10 years was associated with a 40% reduced risk of high-grade prostate cancer.[77] Yet there are only limited clinical data. In a small pilot study, 25 prostate cancer patients followed a low-fat (20% of kilocalories or less), flaxseed-supplemented (30 g/day) diet prior to prostate surgery. Significant decreases in total testosterone, the free androgen index, and the PSA levels were noted among men who had low grade prostate cancer; also observed were lower proliferation rates and significantly higher rates of apoptotic cell death.[78] In the Polyp Prevention Trial, a low fat diet did not significantly alter PSA slope over 4 years.[79] However, it is important to note that this was a secondary, post hoc analysis of men enrolled in a colon study—not a primary prostate cancer prevention trial. In addition, PSA slope is not a valid indicator of incident prostate cancer.

## **Calcium and Dairy**

There is a good deal of prospective epidemiologic evidence suggesting a positive association between intakes of dairy products and calcium intake with prostate cancer risk. Postulated mechanisms include increased levels of circulating insulin-like growth factor-I and decreased circulating levels of the active form of vitamin D (1,25-hydroxyvitamin D).[80, 81]

A meta-analysis of 12 prospective epidemiologic studies demonstrated that men with the highest intakes of dairy products and calcium were more likely to develop prostate cancer and more likely to develop advanced prostate cancer than men with the lowest intakes.[82] The HPFS, the PLCO, and the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study cohorts have observed similar findings.[83-85]

These data are difficult to interpret with regard to clinical applications and patient counseling. Given the substantial benefits of calcium and dairy intake on bone health and reduced colorectal cancer risk [86, 87] and the fact that older men at risk for prostate cancer are also at risk for bony fracture or injury, no definitive recommendations can be made until further data is obtained.

## Zinc

Zinc is an essential mineral abundant in many food sources and a standard component of multivitamins. The concentration of zinc in the prostate is higher than in any other soft tissue in the body. In vitro evidence has suggested that increased zinc is associated with increased prostate cancer risk, possibly through induction of hypoxia inducible factor, which is known to be related to other genitourinary malignancies.[88]

In the HPFS, supplemental zinc intake at doses of up to 100 mg/day was not associated with prostate cancer risk. However, men who consumed more than 100 mg/day of supplemental zinc had more than double the risk of advanced prostate cancer compared to nonusers. The risk was even greater in men who took supplemental zinc for 10 or more years.[89] In the NIH-AARP Diet and Health Study, there was an increased risk of prostate cancer mortality among men with heavy multivitamin use who took zinc supplements. These investigators hypothesize that the negative impact of zinc supplementation may be due to trace elements contained in zinc supplements, such as cadmium, which is a known carcinogen.[90]

## **Conclusions**

While the exact role that diet plays in the incidence and progression of prostate cancer is complex and difficult to isolate from a myriad of genetic and environmental variables, accumulating data on the potential links of diet with prostate cancer are intriguing and merit further study. In particular, therapies that utilize lycopene, soy, cruciferous vegetables, vitamin E, and selenium may offer novel methods for prostate cancer prevention and control. Given the paucity of reliable prospective data regarding diet modification and prostate cancer, it is reasonable to follow the current recommendations of the American Cancer Society [91] and/or the 2007 World Cancer Research Fund Report (<http://wcrf.org>) maintain a well-balanced diet rich in fruits, vegetables, and whole grains; limit red meat; and exercise on a regular basis.

## **Future Perspective**

Epidemiological, pre-clinical, and early clinical data suggest that alterations in diet or nutrient intake may prevent or inhibit prostate cancer. However, there remains a paucity of definitive Level 1 evidence from prospective, randomized clinical trials. A small series of pilot studies have suggested that certain interventions may impact prostate cancer however these studies are severely limited by their size, short intervention period, and the number of interventions performed. (11,12,22,23, 33,34, 67, 76 ) Additionally some of these series use PSA values a secondary endpoints to measure impact on prostate cancer which may or may not be accurate.

To date, there have been no large prospective intervention studies to demonstrate that dietary modifications of micronutrients or macronutrients will alter the natural history or clinical manifestations of prostate cancer. Prostate cancer prevention trials require large numbers of participants and prolonged durations to reach relevant endpoints. Also problematic is the issue of discerning the disparate biological and clinical effects of different foods and food components. The SELECT trial should provide additional insights as to whether vitamin E and/or selenium supplementation will prevent incident prostate cancer. Future studies will focus on clinical trials of diet-based interventions—including high-vegetable diets, dietary fat restriction, and dietary extracts of putative anti-carcinogenic compounds—to determine whether these therapies are efficacious at treating prostate cancer: for example, preventing recurrence after definitive treatment of localized disease, or inhibiting clinical progression in patients enrolled in watchful waiting programs.[28, 35, 92] Future studies will also likely concentrate on identifying diet-related biomarkers in prostate tissue and describing

genomic patterns related to inter-individual variations in physiological and clinical responses to various dietary constituents.

## **Executive Summary**

### **Introduction**

- Accumulating epidemiological and pre-clinical evidence suggests that micronutrients and macronutrients may substantially alter the risk of prostate cancer.

### **Lycopene (Tomato)**

- Lycopene is an antioxidant and free radical scavenger commonly found in tomatoes, watermelon, and grapefruit.
- Several large epidemiologic studies have noted a significantly reduced risk of prostate cancer in those who consume higher quantities of tomato products.

### **Soy**

- Soy is rich in isoflavones and may influence androgen receptor activity and the hormonal milieu.
- Epidemiological studies have consistently observed a decreased risk of prostate cancer with increased soy intake.

### **Cruciferous Vegetables**

- Cruciferous vegetables—including broccoli, broccoli sprouts, cauliflower, radishes, cabbage, brussels sprouts, kale, collard greens, and bok choy—contain a number of potentially anti-carcinogenic substances.

- Although some epidemiologic studies have observed a decreased risk of prostate cancer with higher cruciferous vegetable intake, others have not.

## Vitamin E

- The main dietary sources of vitamin E are vegetable oils;  $\alpha$ -tocopherol is thought to be the most biologically active form and is the form found in dietary supplements.
- Several epidemiological studies have observed a decreased risk of prostate cancer with increased vitamin E intake (400 IU/day).
- The Selenium and Vitamin E Cancer Prevention Trial (SELECT) is a large phase 3 randomized, placebo-controlled trial of selenium and vitamin E supplementation to determine if these compounds decrease the risk of prostate cancer. The anticipated completion date is 2013.

## **Selenium**

- Selenium is believed to influence carcinogenesis through a variety of mechanisms, including androgen receptor signaling modulation, induction of apoptosis, and growth inhibition of prostate cancer cells.
- Increased selenium intake potentially decreases the risk of prostate cancer (200 µgram/day of L-selenomethionine).
- The SELECT trial will further elucidate these associations.

## **Vitamin D**

- Vitamin D may decrease the risk of prostate cancer by promoting apoptosis of prostate cancer cells and modulating expression of a nuclear transcription factor that regulates prostate cell growth and differentiation.
- However, further epidemiological evidence is necessary.

## **β-Carotene**

- β-Carotene can be found in yellow, orange, and green leafy fruits and vegetables and reduces the growth of various prostate cancer cells in vitro.
- Higher intake of β-Carotene and other carotenoids may potentially reduce the risk of prostate cancer.

## **Green Tea**

- Green teas contain substances called catechins, including epigallocatechin (EGCG). EGCG has been demonstrated in vivo to suppress prostate tumor growth and tumor angiogenesis and to promote tumor apoptosis.

- Preliminary epidemiological studies suggest that green tea consumption is associated with a decreased risk of advanced prostate cancer.

### **Pomegranate Juice**

- Compounds in pomegranate juice have potential antioxidant activity and may inhibit prostate cancer cell growth in vitro.
- Pre-clinical and early clinical data are promising but extremely limited and preliminary.
- Epidemiological and definitive clinical evidence are lacking.

### **Meat and Fat**

- There are moderate but inconsistent epidemiological associations of increased meat and fat consumption with elevated risk of prostate cancer.
- Hypotheses to explain these associations include exposure to carcinogenic pesticides, altered hormonal milieus, increased exposure to carcinogenic fatty acids, and increased production of reactive oxygen species.

### **Calcium and Dairy**

- There is much epidemiological evidence to suggest a positive association between intakes of dairy products and calcium intake with increased prostate cancer risk.
- Postulated mechanisms include increased levels of circulating insulin-like growth factor-I and decreased circulating levels of the active form of vitamin D (1,25-hydroxyvitamin D).

- Given the substantial benefits of calcium and dairy intake on bone health and reduced colorectal cancer risk, these data are difficult to interpret with regard to clinical applications and patient counseling.

## **Zinc**

- Zinc is an essential mineral and a standard component of multivitamins. The concentration of zinc in the prostate is higher than in any other soft tissue in the body.
- In vitro evidence has suggested that increased zinc is associated with increased prostate cancer risk, possibly through induction of hypoxia inducible factor.
- Some epidemiological studies have observed increased risk of prostate cancer with increased zinc intake; however, these findings have been inconsistent.

## **Conclusions**

- Accumulating data on the potential links of diet with prostate cancer are intriguing and merit further study.
- Therapies that use lycopene/tomato, soy, cruciferous vegetables, vitamin E, and selenium may offer novel methods for prostate cancer prevention and control.
- Although epidemiological, pre-clinical, and early clinical data suggest that alterations in diet may prevent or inhibit prostate cancer, there remains a paucity of definitive evidence from randomized clinical trials.
- The SELECT trial should provide additional and valuable insights as to whether vitamin E and selenium supplementation will prevent incident prostate cancer.

- Future studies will focus on clinical trials of diet-based interventions to determine whether these therapies are efficacious at preventing and/or treating prostate cancer.

## **References**

- [1] Quinn M, Babb P. Patterns and trends in prostate cancer incidence, survival, prevalence and mortality. Part II: individual countries. *BJU Int.* 2002 Jul;90(2):174-84.
- [2] Saigal CS, Litwin MS. The economic costs of early stage prostate cancer. *Pharmacoeconomics.* 2002;20(13):869-78.
- [3] Campbell JK, Canene-Adams K, Lindshield BL, Boileau TW, Clinton SK, Erdman JW, Jr. Tomato phytochemicals and prostate cancer risk. *J Nutr.* 2004 Dec;134(12 Suppl):3486S-92S.
- [4] Matos HR, Capelozzi VL, Gomes OF, Mascio PD, Medeiros MH. Lycopene inhibits DNA damage and liver necrosis in rats treated with ferric nitrilotriacetate. *Arch Biochem Biophys.* 2001 Dec 15;396(2):171-7.
- [5] Giovannucci E, Ascherio A, Rimm EB, Stampfer MJ, Colditz GA, Willett WC. Intake of carotenoids and retinol in relation to risk of prostate cancer. *J Natl Cancer Inst.* 1995 Dec 6;87(23):1767-76.
- [6] Giovannucci E, Rimm EB, Liu Y, Stampfer MJ, Willett WC. A prospective study of tomato products, lycopene, and prostate cancer risk. *J Natl Cancer Inst.* 2002 Mar 6;94(5):391-8.
- [7] Giovannucci E, Liu Y, Platz EA, Stampfer MJ, Willett WC. Risk factors for prostate cancer incidence and progression in the health professionals follow-up study. *Int J Cancer.* 2007 Oct 1;121(7):1571-8.
- [8] Kirsh VA, Mayne ST, Peters U, Chatterjee N, Leitzmann MF, Dixon LB, et al. A prospective study of lycopene and tomato product intake and risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev.* 2006 Jan;15(1):92-8.

- [9] Kavanaugh CJ, Trumbo PR, Ellwood KC. The U.S. Food and Drug Administration's evidence-based review for qualified health claims: tomatoes, lycopene, and cancer. *J Natl Cancer Inst.* 2007 Jul 18;99(14):1074-85.
- [10] Etminan M, Takkouche B, Caamano-Isorna F. The role of tomato products and lycopene in the prevention of prostate cancer: a meta-analysis of observational studies. *Cancer Epidemiol Biomarkers Prev.* 2004 Mar;13(3):340-5.
- [11] Stacewicz-Sapuntzakis M, Bowen PE. Role of lycopene and tomato products in prostate health. *Biochim Biophys Acta.* 2005 May 30;1740(2):202-5.
- [12] Kucuk O, Sarkar FH, Djuric Z, Sakr W, Pollak MN, Khachik F, et al. Effects of lycopene supplementation in patients with localized prostate cancer. *Exp Biol Med (Maywood).* 2002 Nov;227(10):881-5.
- [13] Perabo FG, Von Low EC, Ellinger J, von Rucker A, Muller SC, Bastian PJ. Soy isoflavone genistein in prevention and treatment of prostate cancer. *Prostate Cancer Prostatic Dis.* 2008;11(1):6-12.
- [14] Hamilton-Reeves JM, Rebello SA, Thomas W, Slaton JW, Kurzer MS. Isoflavone-rich soy protein isolate suppresses androgen receptor expression without altering estrogen receptor-beta expression or serum hormonal profiles in men at high risk of prostate cancer. *J Nutr.* 2007 Jul;137(7):1769-75.
- [15] Von Low EC, Perabo FG, Siener R, Muller SC. Review. Facts and fiction of phytotherapy for prostate cancer: a critical assessment of preclinical and clinical data. *In Vivo.* 2007 Mar-Apr;21(2):189-204.

- [16] Ouchi H, Ishiguro H, Ikeda N, Hori M, Kubota Y, Uemura H. Genistein induces cell growth inhibition in prostate cancer through the suppression of telomerase activity. Int J Urol. 2005 Jan;12(1):73-80.
- [17] Jacobsen BK, Knutson SF, Fraser GE. Does high soy milk intake reduce prostate cancer incidence? The Adventist Health Study (United States). Cancer Causes Control. 1998 Dec;9(6):553-7.
- [18] Yan L, Spitznagel EL. Meta-analysis of soy food and risk of prostate cancer in men. Int J Cancer. 2005 Nov 20;117(4):667-9.
- [19] Kumar NB, Cantor A, Allen K, Riccardi D, Besterman-Dahan K, Seigne J, et al. The specific role of isoflavones in reducing prostate cancer risk. Prostate. 2004 May 1;59(2):141-7.
- [20] deVere White RW, Hackman RM, Soares SE, Beckett LA, Li Y, Sun B. Effects of a genistein-rich extract on PSA levels in men with a history of prostate cancer. Urology. 2004 Feb;63(2):259-63.
- [21] Dalais FS, Meliala A, Wattanapenpaiboon N, Frydenberg M, Suter DA, Thomson WK, et al. Effects of a diet rich in phytoestrogens on prostate-specific antigen and sex hormones in men diagnosed with prostate cancer. Urology. 2004 Sep;64(3):510-5.
- [22] Schroder FH, Roobol MJ, Boeve ER, de Mutsert R, Zuidgeest-van Leeuwen SD, Kersten I, et al. Randomized, double-blind, placebo-controlled crossover study in men with prostate cancer and rising PSA: effectiveness of a dietary supplement. Eur Urol. 2005 Dec;48(6):922-30; discussion 30-1.

- [23] Grainger EM, Schwartz SJ, Wang S, Unlu NZ, Boileau TW, Ferketich AK, et al. A combination of tomato and soy products for men with recurring prostate cancer and rising prostate specific antigen. *Nutr Cancer*. 2008 Mar-Apr;60(2):145-54.
- [24] Aggarwal BB, Ichikawa H. Molecular targets and anticancer potential of indole-3-carbinol and its derivatives. *Cell Cycle*. 2005 Sep;4(9):1201-15.
- [25] Brooks JD, Paton V. Potent induction of carcinogen defence enzymes with sulforaphane, a putative prostate cancer chemopreventive agent. *Prostate Cancer Prostatic Dis*. 1999 Nov;2(S3):S8.
- [26] Brooks JD, Paton VG, Vidanes G. Potent induction of phase 2 enzymes in human prostate cells by sulforaphane. *Cancer Epidemiol Biomarkers Prev*. 2001 Sep;10(9):949-54.
- [27] Singh AV, Xiao D, Lew KL, Dhir R, Singh SV. Sulforaphane induces caspase-mediated apoptosis in cultured PC-3 human prostate cancer cells and retards growth of PC-3 xenografts in vivo. *Carcinogenesis*. 2004 Jan;25(1):83-90.
- [28] Caruso AJ, Yegnasubramanian S, Lin X, Kesler TW, Nelson WG. Hot water extracts from broccoli sprouts trigger induction of carcinogen-detoxification enzymes in prostate tissues. American Association for Cancer Research 95th Annual Meeting; 2004; Orlando, FL; 2004. p. 729.
- [29] Canene-Adams K, Lindshield BL, Wang S, Jeffery EH, Clinton SK, Erdman JW, Jr. Combinations of tomato and broccoli enhance antitumor activity in dunning r3327-h prostate adenocarcinomas. *Cancer Res*. 2007 Jan 15;67(2):836-43.

- [30] Kirsh VA, Peters U, Mayne ST, Subar AF, Chatterjee N, Johnson CC, et al. Prospective study of fruit and vegetable intake and risk of prostate cancer. *J Natl Cancer Inst.* 2007 Aug 1;99(15):1200-9.
- [31] Giovannucci E, Rimm EB, Liu Y, Stampfer MJ, Willett WC. A prospective study of cruciferous vegetables and prostate cancer. *Cancer Epidemiol Biomarkers Prev.* 2003 Dec;12(12):1403-9.
- [32] Key TJ, Allen N, Appleby P, Overvad K, Tjønneland A, Miller A, et al. Fruits and vegetables and prostate cancer: no association among 1104 cases in a prospective study of 130544 men in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Int J Cancer.* 2004 Mar;109(1):119-24.
- [33] Ornish D, Weidner G, Fair WR, Marlin R, Pettengill EB, Raisin CJ, et al. Intensive lifestyle changes may affect the progression of prostate cancer. *J Urol.* 2005 Sep;174(3):1065-9; discussion 9-70.
- [34] Ornish D, Magbanua MJ, Weidner G, Weinberg V, Kemp C, Green C, et al. Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention. *Proc Natl Acad Sci U S A.* 2008 Jun 17;105(24):8369-74.
- [35] Parsons JK, Newman V, Mohler JL, Pierce JP, Paskett E, Marshall J. The Men's Eating and Living (MEAL) Study: A Cancer and Leukemia Group B Pilot Trial of Dietary Intervention for the Treatment of Prostate Cancer. *Urology.* 2008 Feb 14.
- [36] Cheung E, Wadhera P, Dorff T, Pinski J. Diet and prostate cancer risk reduction. *Expert Rev Anticancer Ther.* 2008 Jan;8(1):43-50.
- [37] Crispen PL, Uzzo RG, Golovine K, Makhov P, Pollack A, Horwitz EM, et al. Vitamin E succinate inhibits NF-kappaB and prevents the development of a metastatic

phenotype in prostate cancer cells: implications for chemoprevention. *Prostate*. 2007 May 1;67(6):582-90.

[38] Venkateswaran V, Fleshner NE, Klotz LH. Modulation of cell proliferation and cell cycle regulators by vitamin E in human prostate carcinoma cell lines. *J Urol*. 2002 Oct;168(4 Pt 1):1578-82.

[39] Shiau CW, Huang JW, Wang DS, Weng JR, Yang CC, Lin CH, et al. alpha-Tocopheryl succinate induces apoptosis in prostate cancer cells in part through inhibition of Bcl-xL/Bcl-2 function. *J Biol Chem*. 2006 Apr 28;281(17):11819-25.

[40] Heinonen OP, Albanes D, Virtamo J, Taylor PR, Huttunen JK, Hartman AM, et al. Prostate cancer and supplementation with alpha-tocopherol and beta-carotene: incidence and mortality in a controlled trial. *J Natl Cancer Inst*. 1998 Mar 18;90(6):440-6.

[41] Chan JM, Stampfer MJ, Ma J, Rimm EB, Willett WC, Giovannucci EL. Supplemental vitamin E intake and prostate cancer risk in a large cohort of men in the United States. *Cancer Epidemiol Biomarkers Prev*. 1999 Oct;8(10):893-9.

[42] Kirsh VA, Hayes RB, Mayne ST, Chatterjee N, Subar AF, Dixon LB, et al. Supplemental and dietary vitamin E, beta-carotene, and vitamin C intakes and prostate cancer risk. *J Natl Cancer Inst*. 2006 Feb 15;98(4):245-54.

[43] Wright ME, Weinstein SJ, Lawson KA, Albanes D, Subar AF, Dixon LB, et al. Supplemental and dietary vitamin E intakes and risk of prostate cancer in a large prospective study. *Cancer Epidemiol Biomarkers Prev*. 2007 Jun;16(6):1128-35.

- [44] Lippman SM, Goodman PJ, Klein EA, Parnes HL, Thompson IM, Jr., Kristal AR, et al. Designing the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *J Natl Cancer Inst.* 2005 Jan 19;97(2):94-102.
- [45] Yamaguchi K, Uzzo RG, Pimkina J, Makhov P, Golovine K, Crispen P, et al. Methylseleninic acid sensitizes prostate cancer cells to TRAIL-mediated apoptosis. *Oncogene.* 2005 Sep 1;24(38):5868-77.
- [46] Lee SO, Yeon Chun J, Nadiminty N, Trump DL, Ip C, Dong Y, et al. Monomethylated selenium inhibits growth of LNCaP human prostate cancer xenograft accompanied by a decrease in the expression of androgen receptor and prostate-specific antigen (PSA). *Prostate.* 2006 Jul 1;66(10):1070-5.
- [47] Clark LC, Combs GF, Jr., Turnbull BW, Slate EH, Chalker DK, Chow J, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. *Jama.* 1996 Dec 25;276(24):1957-63.
- [48] Duffield-Lillico AJ, Slate EH, Reid ME, Turnbull BW, Wilkins PA, Combs GF, Jr., et al. Selenium supplementation and secondary prevention of nonmelanoma skin cancer in a randomized trial. *J Natl Cancer Inst.* 2003 Oct 1;95(19):1477-81.
- [49] Etminan M, FitzGerald JM, Gleave M, Chambers K. Intake of selenium in the prevention of prostate cancer: a systematic review and meta-analysis. *Cancer Causes Control.* 2005 Nov;16(9):1125-31.
- [50] Syed DN, Khan N, Afaq F, Mukhtar H. Chemoprevention of prostate cancer through dietary agents: progress and promise. *Cancer Epidemiol Biomarkers Prev.* 2007 Nov;16(11):2193-203.

- [51] Ingraham BA, Bragdon B, Nohe A. Molecular basis of the potential of vitamin D to prevent cancer. *Curr Med Res Opin.* 2008 Jan;24(1):139-49.
- [52] Colli JL, Colli A. International comparisons of prostate cancer mortality rates with dietary practices and sunlight levels. *Urol Oncol.* 2006 May-Jun;24(3):184-94.
- [53] Schwartz GG, Hanchette CL. UV, latitude, and spatial trends in prostate cancer mortality: all sunlight is not the same (United States). *Cancer Causes Control.* 2006 Oct;17(8):1091-101.
- [54] Vieth R, Choo R, Deboer L, Danjoux C, Morton GC, Klotz L. Rise in prostate-specific antigen in men with untreated low-grade prostate cancer is slower during spring-summer. *Am J Ther.* 2006 Sep-Oct;13(5):394-9.
- [55] Tavani A, Bertuccio P, Bosetti C, Talamini R, Negri E, Franceschi S, et al. Dietary intake of calcium, vitamin D, phosphorus and the risk of prostate cancer. *Eur Urol.* 2005 Jul;48(1):27-33.
- [56] Ahn J, Peters U, Albanes D, Purdue MP, Abnet CC, Chatterjee N, et al. Serum vitamin D concentration and prostate cancer risk: a nested case-control study. *J Natl Cancer Inst.* 2008 Jun 4;100(11):796-804.
- [57] Chan JM, Gann PH, Giovannucci EL. Role of diet in prostate cancer development and progression. *J Clin Oncol.* 2005 Nov 10;23(32):8152-60.
- [58] Giovannucci E, Liu Y, Rimm EB, Hollis BW, Fuchs CS, Stampfer MJ, et al. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. *J Natl Cancer Inst.* 2006 Apr 5;98(7):451-9.

- [59] Williams AW, Boileau TW, Zhou JR, Clinton SK, Erdman JW, Jr. Beta-carotene modulates human prostate cancer cell growth and may undergo intracellular metabolism to retinol. *J Nutr.* 2000 Apr;130(4):728-32.
- [60] Key TJ, Appleby PN, Allen NE, Travis RC, Roddam AW, Jenab M, et al. Plasma carotenoids, retinol, and tocopherols and the risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition study. *Am J Clin Nutr.* 2007 Sep;86(3):672-81.
- [61] Virtamo J, Pietinen P, Huttunen JK, Korhonen P, Malila N, Virtanen MJ, et al. Incidence of cancer and mortality following alpha-tocopherol and beta-carotene supplementation: a postintervention follow-up. *Jama.* 2003 Jul 23;290(4):476-85.
- [62] Hennekens CH, Buring JE, Manson JE, Stampfer M, Rosner B, Cook NR, et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med.* 1996 May 2;334(18):1145-9.
- [63] Cook NR, Stampfer MJ, Ma J, Manson JE, Sacks FM, Buring JE, et al. Beta-carotene supplementation for patients with low baseline levels and decreased risks of total and prostate carcinoma. *Cancer.* 1999 Nov 1;86(9):1783-92.
- [64] Siddiqui IA, Adhami VM, Saleem M, Mukhtar H. Beneficial effects of tea and its polyphenols against prostate cancer. *Mol Nutr Food Res.* 2006 Feb;50(2):130-43.
- [65] Yang CS, Lambert JD, Ju J, Lu G, Sang S. Tea and cancer prevention: molecular mechanisms and human relevance. *Toxicol Appl Pharmacol.* 2007 Nov 1;224(3):265-73.

- [66] Kurahashi N, Sasazuki S, Iwasaki M, Inoue M, Tsugane S. Green tea consumption and prostate cancer risk in Japanese men: a prospective study. *Am J Epidemiol.* 2008 Jan 1;167(1):71-7.
- [67] Malik A, Afaq F, Sarfaraz S, Adhami VM, Syed DN, Mukhtar H. Pomegranate fruit juice for chemoprevention and chemotherapy of prostate cancer. *Proc Natl Acad Sci U S A.* 2005 Oct 11;102(41):14813-8.
- [68] Sartippour MR, Seeram NP, Rao JY, Moro A, Harris DM, Henning SM, et al. Ellagitannin-rich pomegranate extract inhibits angiogenesis in prostate cancer in vitro and in vivo. *Int J Oncol.* 2008 Feb;32(2):475-80.
- [69] Hong MY, Seeram NP, Heber D. Pomegranate polyphenols down-regulate expression of androgen-synthesizing genes in human prostate cancer cells overexpressing the androgen receptor. *J Nutr Biochem.* 2008 May 12.
- [70] Pantuck AJ, Leppert JT, Zomorodian N, Aronson W, Hong J, Barnard RJ, et al. Phase II study of pomegranate juice for men with rising prostate-specific antigen following surgery or radiation for prostate cancer. *Clin Cancer Res.* 2006 Jul 1;12(13):4018-26.
- [71] Schuurman AG, van den Brandt PA, Dorant E, Brants HA, Goldbohm RA. Association of energy and fat intake with prostate carcinoma risk: results from The Netherlands Cohort Study. *Cancer.* 1999 Sep 15;86(6):1019-27.
- [72] Fleshner N, Zlotta AR. Prostate cancer prevention: past, present, and future. *Cancer.* 2007 Nov 1;110(9):1889-99.
- [73] Fleshner N, Bagnell PS, Klotz L, Venkateswaran V. Dietary fat and prostate cancer. *J Urol.* 2004 Feb;171(2 Pt 2):S19-24.

- [74] Rodriguez C, McCullough ML, Mondul AM, Jacobs EJ, Chao A, Patel AV, et al. Meat consumption among Black and White men and risk of prostate cancer in the Cancer Prevention Study II Nutrition Cohort. *Cancer Epidemiol Biomarkers Prev.* 2006 Feb;15(2):211-6.
- [75] Crowe FL, Key TJ, Appleby PN, Travis RC, Overvad K, Jakobsen MU, et al. Dietary fat intake and risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition. *Am J Clin Nutr.* 2008 May;87(5):1405-13.
- [76] Park SY, Murphy SP, Wilkens LR, Henderson BE, Kolonel LN. Fat and meat intake and prostate cancer risk: the multiethnic cohort study. *Int J Cancer.* 2007 Sep 15;121(6):1339-45.
- [77] Rodriguez C, Freedland SJ, Deka A, Jacobs EJ, McCullough ML, Patel AV, et al. Body Mass Index, Weight Change, and Risk of Prostate Cancer in the Cancer Prevention Study II Nutrition Cohort. *Cancer Epidemiol Biomarkers Prev.* 2006 Dec 19.
- [78] Demark-Wahnefried W, Price DT, Polascik TJ, Robertson CN, Anderson EE, Paulson DF, et al. Pilot study of dietary fat restriction and flaxseed supplementation in men with prostate cancer before surgery: exploring the effects on hormonal levels, prostate-specific antigen, and histopathologic features. *Urology.* 2001 Jul;58(1):47-52.
- [79] Shike M, Latkany L, Riedel E, Fleisher M, Schatzkin A, Lanza E, et al. Lack of effect of a low-fat, high-fruit, -vegetable, and -fiber diet on serum prostate-specific antigen of men without prostate cancer: results from a randomized trial. *J Clin Oncol.* 2002 Sep 1;20(17):3592-8.

- [80] Holmes MD, Pollak MN, Willett WC, Hankinson SE. Dietary correlates of plasma insulin-like growth factor I and insulin-like growth factor binding protein 3 concentrations. *Cancer Epidemiol Biomarkers Prev.* 2002 Sep;11(9):852-61.
- [81] Giovannucci E. Dietary influences of 1,25(OH)2 vitamin D in relation to prostate cancer: a hypothesis. *Cancer Causes Control.* 1998 Dec;9(6):567-82.
- [82] Gao X, LaValley MP, Tucker KL. Prospective studies of dairy product and calcium intakes and prostate cancer risk: a meta-analysis. *J Natl Cancer Inst.* 2005 Dec 7;97(23):1768-77.
- [83] Giovannucci E, Liu Y, Stampfer MJ, Willett WC. A prospective study of calcium intake and incident and fatal prostate cancer. *Cancer Epidemiol Biomarkers Prev.* 2006 Feb;15(2):203-10.
- [84] Ahn J, Albanes D, Peters U, Schatzkin A, Lim U, Freedman M, et al. Dairy products, calcium intake, and risk of prostate cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. *Cancer Epidemiol Biomarkers Prev.* 2007 Dec;16(12):2623-30.
- [85] Mitrou PN, Albanes D, Weinstein SJ, Pietinen P, Taylor PR, Virtamo J, et al. A prospective study of dietary calcium, dairy products and prostate cancer risk (Finland). *Int J Cancer.* 2007 Jun 1;120(11):2466-73.
- [86] Welten DC, Kemper HC, Post GB, van Staveren WA. A meta-analysis of the effect of calcium intake on bone mass in young and middle aged females and males. *J Nutr.* 1995 Nov;125(11):2802-13.

- [87] Cho E, Smith-Warner SA, Spiegelman D, Beeson WL, van den Brandt PA, Colditz GA, et al. Dairy foods, calcium, and colorectal cancer: a pooled analysis of 10 cohort studies. *J Natl Cancer Inst.* 2004 Jul 7;96(13):1015-22.
- [88] Park SE, Park JW, Cho YS, Ryu JH, Paick JS, Chun YS. HIF-1alpha promotes survival of prostate cells at a high zinc environment. *Prostate.* 2007 Oct 1;67(14):1514-23.
- [89] Leitzmann MF, Stampfer MJ, Wu K, Colditz GA, Willett WC, Giovannucci EL. Zinc supplement use and risk of prostate cancer. *J Natl Cancer Inst.* 2003 Jul 2;95(13):1004-7.
- [90] Lawson KA, Wright ME, Subar A, Mouw T, Hollenbeck A, Schatzkin A, et al. Multivitamin use and risk of prostate cancer in the National Institutes of Health-AARP Diet and Health Study. *J Natl Cancer Inst.* 2007 May 16;99(10):754-64.
- [91] Doyle C, Kushi LH, Byers T, Courneya KS, Demark-Wahnefried W, Grant B, et al. Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices. *CA Cancer J Clin.* 2006 Nov-Dec;56(6):323-53.
- [92] Parsons JK, Newman VA, Mohler JL, Pierce JP, Flatt S, Marshall J. Dietary modification in patients with prostate cancer on active surveillance: a randomized, multicentre feasibility study. *BJU Int.* 2008 Jan 24.

**Dietary Intervention After  
Definitive Therapy for Localized Prostate Cancer:  
Results from a Pilot Study**

J. Kellogg Parsons,<sup>1-3</sup> Vicky A. Newman,<sup>2</sup> James L. Mohler,<sup>4</sup>  
John P. Pierce,<sup>2</sup> Shirley Flatt,<sup>2</sup> Karen Messer,<sup>2</sup> and James Marshall<sup>4</sup>

<sup>1</sup>UCSD Medical Center, San Diego, CA

<sup>2</sup>Moores Comprehensive Cancer Center, University of California San Diego

3855 Health Sciences Drive  
La Jolla, CA 92093-0901  
Tel: 858-822-0175  
Fax: 858-822-0025

<sup>3</sup>Veterans Affairs San Diego Medical Center

3350 La Jolla Village Drive  
San Diego, CA 92161  
Tel: 858-552-8585  
Fax: 858-552-7452

<sup>4</sup>Roswell Park Cancer Institute, Buffalo, New York

Elm and Carlton Streets  
Buffalo, NY 14263  
Tel: 716 845-8444  
Fax: 716 845-8487

**Correspondence:**

J. Kellogg Parsons, MD, MHS  
c/o Leslie Parker  
UCSD Division of Urology  
200 West Arbor Drive #8897  
San Diego, CA 92103-8897  
Tel: 619-543-2630  
Fax: 619-543-6573  
[lepark@ucsd.edu](mailto:lepark@ucsd.edu)

**Funding for this study was provided by Cancer and Leukemia Group B and the Darrow Foundation.**

**Conflict of Interest: none**

## **Abstract**

INTRODUCTION: Diet has been linked to prostate cancer risk. Dietary modification may inhibit prostate cancer progression.

MATERIALS AND METHODS: As part of a randomized trial, we analyzed the effect of a diet-based intervention on 25 prostate cancer patients who had previously undergone surgery or radiation.

RESULTS AND CONCLUSIONS: In the intervention arm, vegetable intake increased ( $P <0.05$ ), fat intake decreased ( $P <0.05$ ), and mean plasma levels of  $\beta$ -carotene and total carotenoids increased ( $P <0.05$ ). In the control arm, there were no significant changes in diet or blood carotenoids. These data support the feasibility of studying dietary interventions as salvage or adjuvant therapy after surgery or radiation for localized prostate cancer.

**Key Words:** diet; surveillance; broccoli; lycopene; crucifer; surgery; radiation; radical prostatectomy; brachytherapy

## **Introduction**

Up to 50% of newly diagnosed prostate cancer patients present with clinically localized disease;<sup>[1]</sup> most receive definitive therapy with surgery or radiation.<sup>[2]</sup> The estimated incidence of prostate-specific antigen (PSA) recurrence following definitive therapy, 70 000 patients per year,<sup>[3]</sup> corresponds to a likely U.S. population prevalence of at least several hundred thousand. The scope of this problem calls for the development of innovative therapies to treat PSA-only recurrence.

Rapid PSA rises following definitive therapy, measured as low PSA doubling times (PSADT), are associated with increased prostate cancer–specific mortality.<sup>[4,5]</sup> Most investigators agree that patients with rapidly rising PSA following definitive therapy are candidates for local and systemic salvage therapies.

However, most patients with PSA-only recurrence do not experience rapidly rising PSA; rather, these patients evince slow rises and prolonged, asymptomatic clinical courses.<sup>[4]</sup> Although salvage therapies—including radiation, radical prostatectomy, cryosurgery, and androgen deprivation—potentially increase progression-free survival after definitive therapy in select patients,<sup>[3,6]</sup> they are also associated with side effects that may substantially diminish quality of life. Moreover, there is scant evidence to support definitive survival benefits for salvage therapy in patients with slowly rising PSA.

A novel approach with minimal toxicity is dietary modification. Epidemiological studies suggest that diets high in vegetables and low in fat, meat, and dairy products may protect against prostate cancer and decrease the risk of progression.<sup>[7-9]</sup> In vitro models demonstrate that components of cruciferous vegetables (isothiocyanates) and

tomatoes (lycopene) induce apoptosis of prostate cancer cells, inhibit carcinogenesis, and promote the expression of cytoprotective enzymes.[10-12]

Clinical evidence supporting these observational and preclinical findings remains limited. In the only dietary study to date in patients with PSA recurrence after definitive therapy, PSADT significantly increased 6 months after patients began a program of diet modification and stress reduction.[13] However, this study was small and nonrandomized and included substantial lifestyle modifications. Thus, these results cannot with certainty be attributed to changes in nutritional intake. Further studies of dietary interventions for PSA recurrence are needed, particularly since many prostate cancer patients are already experimenting with diet and dietary supplements.[14,15]

We previously designed and implemented a telephone-based dietary intervention for breast cancer patients; the intervention produced significant, long-lasting diet changes in these patients.[16] We adapted this method for men with prostate cancer and tested it in a randomized, multicenter pilot trial: The Men's Eating and Living (MEAL) Study.[17] To evaluate the feasibility of studying diet-based interventions following definitive therapy for prostate cancer, we analyzed the efficacy of this intervention to effect diet change in a cohort of MEAL participants who had undergone surgery or radiation.

## **Materials and Methods**

### *Participants*

The MEAL Study was conducted at 4 clinical sites of the Cancer and Leukemia Group B Cooperative Study Group: The James Cancer Center of Ohio State University,

the Southern Medical Oncology Consortium, the Moores UCSD Cancer Center of the University of California at San Diego, and the Roswell Park Cancer Institute (RPCI). The major enrollment sites were UCSD and RPCI. Institutional review board approval was obtained at all study sites.

Eligible patients were men aged 50 to 80 years with biopsy-proven prostate cancer. Other inclusion criteria were no history of other malignancy (other than nonmelanoma skin cancer) in the previous 5 years and life expectancy  $\geq$  3 years. Exclusion criteria included psychiatric illness precluding compliance with the intervention and/or obtainment of informed consent; medical conditions that would make the protocol unreasonably hazardous; intolerance to cruciferous vegetables and/or tomato products; and metastatic prostate cancer.

A total of 74 prostate cancer patients were recruited between March 2005 and March 2006. Of these, 25 (34%) had undergone prior treatment with surgery or radiation. Data collection was completed November 30, 2006.

#### *Study design*

MEAL was a 6-month, randomized, controlled clinical trial. The randomization ratio was 2:1 (intervention to control). Participants were randomized to an intervention of structured dietary education and telephone-based counseling promoting 7 or more servings of vegetables a day, with decreased fat and red meat intake; or to a control condition that provided print materials with standard guidelines recommending 5 servings of vegetables and fruits daily (U.S. Department of Agriculture, National Cancer Institute, and American Cancer Society). All counseling, performed by telephone from

the Moores UCSD Cancer Center, utilized a stepwise, phased approach employing social cognitive theory and motivational interviewing techniques as previously described.[17]

#### *Outcomes assessment*

Diets were evaluated at baseline and 6 months, each by a series of 3 separate 24-hour dietary recalls collected interactively via telephone interview. Data were catalogued and analyzed utilizing Minnesota Nutrition Data System (NDS) software (Nutrition Coordinating Center, University of Minnesota). Blood samples were collected at baseline and at 6 months and analyzed for plasma carotenoid and serum PSA concentrations. The primary outcome variables were the differences in dietary intakes and plasma carotenoid concentrations between baseline and 6 months (within and between groups).

#### *Statistical Analyses*

Changes in mean self-reported intake of total vegetables, cruciferous vegetables, tomato products, lettuce and potatoes, other vegetables, fruit, whole grains, beans/legumes, fiber, and fat were compared using paired *t* tests within each group and 2 sample *t* tests between groups. Baseline carotenoid values, log transformed to improve normality, were examined for group differences. Changes in measured plasma α-carotene, β-carotene, lutein, lycopene, beta-cryptoxanthin, and total carotenoids were compared using paired *t* tests within each group and 2 sample *t* tests between groups.

## **Results**

## *Participants*

Of the 25 participants who had undergone prior surgery or radiation, 17 (68%) had undergone radical prostatectomy, 5 (20%) radiotherapy with androgen deprivation, and 3 (12%) brachytherapy (Table 1). Three (12%) were lost to follow-up prior to 6-month data collection (Figure 1).

## *Dietary changes: vegetables*

Vegetable intakes in the intervention arm increased significantly at 6 months, while those in the control arm remained static (Table 2). In the intervention arm, mean daily intakes of total vegetables, crucifers, tomato products, and other vegetables increased by 70%, 52%, 237%, and 45%, respectively, while lettuce and potato intake decreased by 61% ( $P<0.05$ ). In the control arm, there were no significant changes in mean intakes of total vegetables, tomato products, crucifers, lettuce and potatoes, or other vegetables. Compared to control, the increases in total vegetables, tomatoes, and other vegetables in the intervention arm were significant ( $P<0.05$ ).

## *Dietary changes: fat*

Fat intake decreased by 17% ( $P<0.05$ ) in the intervention arm and remained stable in the control arm (Table 2).

## *Plasma carotenoid concentrations*

Carotenoid concentrations increased in the intervention arm but not in the control arm (Table 3). At baseline, plasma total carotenoid concentrations of intervention and

control participants were similar. At 6 months, the mean total concentration had risen in intervention participants by a significant 19% ( $P<0.05$ ) and in controls by a nonsignificant 2%. In the intervention arm, the mean  $\beta$ -carotene concentration increased by 35% ( $P<0.05$ ), while mean concentrations of  $\alpha$ -carotene, lutein, lycopene, and cryptoxanthin concentrations did not change significantly. In the control arm, there were no significant changes in any of the carotenoids measured (Table 3).

#### *PSA concentrations*

Plasma PSA concentrations at baseline and 6 months were available for 22 of the 25 participants (Table 1). There were only 10 patients with PSA levels that changed across the 3 treatment types and 2 study conditions. Thus, the small size of the dataset precluded definitive quantitative analyses of PSA.

## **Discussion**

Assessing the clinical efficacy of dietary change in prostate cancer patients requires carefully designed clinical trials focused on feasible dietary interventions. The intensive lifestyle modifications and face-to-face counseling employed in prior interventions[13,18] require substantial resource commitments that may be difficult to implement and sustain in larger patient populations. In contrast, the intervention we describe is practicable, easy to implement, and centralized. It demands few resource commitments and is relatively low cost, even for relatively large study samples.

To our knowledge, this is the first clinical trial to investigate the application of a validated, diet-based intervention as a potential form of adjuvant or salvage therapy for

prostate cancer following definitive therapy for localized disease. These pilot data suggest that telephone-based counseling emphasizing a plant-based diet significantly increases vegetable intake, decreases fat intake, and increases plasma concentrations of potentially anticarcinogenic carotenoids in prostate cancer patients who have previously undergone definitive local therapy.

This intervention focuses on dietary components associated with decreased prostate cancer incidence and progression. The telephone counseling protocol focused on helping men set serial dietary change goals that were achievable within their lifestyle (sometimes their spouse was on the phone as well).[19] Counselors also framed positively [20] the effort put into achieving these goals so as to optimize self-efficacy.[21] Patient-centered counseling approaches were used to maintain motivation,[2] to modify lifestyles for longer-term inclusion of these dietary changes, and to promote retention in the study. A similar program has produced significant diet changes and plasma carotenoid increases for at least 4 years in more than 1 500 breast cancer patients who continued periodic counseling.[16]

Diet change represents an innovative approach to refining current treatment paradigms for PSA-only recurrence after definitive therapy. It is unclear whether the morbidities of salvage therapies outweigh potential survival benefits in patients with less aggressive disease as indicated by longer PSADT. In this sense, a plant-based dietary intervention represents a compelling salvage option for these patients. Other potential applications of this dietary intervention are as adjuvant treatment in patients with low- to intermediate-risk disease, adjuvant treatment in patients with high-risk disease who decline more aggressive forms of therapy, and primary treatment in active surveillance.

Prostate cancer diagnosis is a source of considerable anxiety and diminished quality of life for many prostate cancer patients, even after definitive therapy.[22-24] Dietary change could quell anxiety, improve quality of life, and encourage men with higher PSADT and no other clinical signs of progression to eschew or delay adjuvant, morbidity-generating therapies with unproven survival benefits. Since these patients are usually asymptomatic, they would likely be receptive to nutritional interventions with proven benefits to cardiovascular and overall health. Indeed, it is likely that many—if not most—older patients with a slow rising PSA will die of cardiovascular disease rather than metastatic prostate cancer. Future dietary intervention trials should thus consider major coronary events (myocardial infarction, coronary artery bypass surgery, angioplasty, and stroke) as important secondary endpoints.

Although dietary self-reporting methods may be susceptible to systematic measurement error,[25] plasma carotenoid concentrations are an effective biomarker for dietary intake of carotenoids and serve as an objective indicator of a vegetable-intense diet.[26] The increases in blood carotenoid concentrations in the intervention patients validate the participant-reported dietary changes. Moreover, carotenoids have been associated with reduced risk of incident prostate cancer[27,28] and diminished oxidative damage in prostate tissue.[29] Total carotenoid concentrations increased 19% in the intervention group. However, there was not a significant increase in plasma lycopene, even though these men reported major increases in tomato consumption. In observational and feeding studies that have examined the relationship between vegetable and fruit intake and plasma carotenoid concentrations, lycopene is typically not as responsive to or as correlated with vegetable and fruit intake, compared to the

other carotenoids.[30] Compared to the other carotenoids, lycopene is found in abundance in few foods—mainly tomatoes and tomato products, watermelon, and pink grapefruit—and when these foods are consumed in raw form, the concentration and dosage is relatively low because of the dilution factor. When cooked, such as in the production of tomato sauce or paste, the amount of lycopene per serving is increased, which explains why those cooked and concentrated sources typically are more predictive of plasma lycopene concentration than raw tomatoes or overall vegetable and fruit intake.[31]

Two limitations of this analysis merit discussion. First, these results do not prove that the changes in diet intake and plasma carotenoid concentrations observed over a 6-month period will be maintained over a longer period of time. Nevertheless, our experience with the prior study in breast cancer patients[16] suggests that diet changes observed in the first 6 months of the MEAL intervention could be maintained for at least 4 years should the intervention continue.

Second, these results do not prove that changes in diet and plasma carotenoid concentrations will necessarily alter the natural history of PSA-only recurrence. Our intent in this feasibility study was to test whether a telephone-based counseling intervention would produce diet and plasma carotenoid changes in prostate cancer patients, including those who have previously undergone definitive local therapy—not to assess whether these changes would alter clinical progression. The rationale for trials of diet intervention and prostate cancer is driven not only by the possibility that diet plays a significant role in prostate cancer carcinogenesis, but also by the widespread desire of patients to know whether dietary change has any value in disease control.

In summary, these data support the feasibility of implementing clinical trials of dietary interventions in men with prostate cancer following definitive therapy. Our findings warrant additional randomized clinical trials to further test this intervention. Future, larger studies should utilize PSA changes as a primary endpoint to test the hypothesis that telephone-based diet changes will diminish disease progression and the need for conventional salvage or adjuvant treatments in these patients.

## **Acknowledgements**

The authors would like to acknowledge the contributions of Leslie Barbier for her efforts in recruitment and retention of study participants; the MEAL UCSD Counseling Team (Joyce Bertaux, Sharon Bonner, Sheila Fisher, Prudy Galagan, Pam Herkovitz) for the critical role they played in facilitating dietary behavior change in the intervention group; and the MEAL study participants.

## References

1. Cooperberg MR, Lubeck DP, Meng MV, Mehta SS, Carroll PR. The changing face of low-risk prostate cancer: trends in clinical presentation and primary management. *J Clin Oncol* 2004; **22**:2141-2149.
2. Miller DC, Gruber SB, Hollenbeck BK, Montie JE, Wei JT. Incidence of initial local therapy among men with lower-risk prostate cancer in the United States. *J Natl Cancer Inst* 2006; **98**:1134-1141.
3. Freedland SJ, Moul JW. Prostate specific antigen recurrence after definitive therapy. *J Urol* 2007; **177**:1985-1991.
4. Freedland SJ, Humphreys EB, Mangold LA, Eisenberger M, Dorey FJ, Walsh PC, et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. *JAMA* 2005; **294**:433-439.
5. D'Amico AV, Moul JW, Carroll PR, Sun L, Lubeck DP, Chen MH. Surrogate end point for prostate cancer-specific mortality after radical prostatectomy or radiation therapy. *JNCI* 2003; **95**:1352-1353.
6. Stephenson AJ, Shariat SF, Zelefsky MJ, Kattan MW, Butler EB, Tin BS, et al. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. *JAMA* 2004; **291**:1325-1332.
7. Sonn GA, Aronson W, Litwin MS. Impact of diet on prostate cancer: a review. *Prostate Cancer Prostatic Dis* 2005; **8**:304-310.
8. Stevens VL, Rodriguez C, Pavluck AL, McCullough ML, Thun MJ, Calle EE. Folate nutrition and prostate cancer incidence in a large cohort of US men. *Am J Epidemiol* 2006; **163**:989-996.

9. Cohen JH, Kristal AR, Stanford JL. Fruit and vegetable intakes and prostate cancer risk. *J Natl Cancer Inst* 2000; **92**:61-68.
10. Barber NJ, Zhang X, Zhu G, Pramanik R, Barber JA, Martin FL, et al. Lycopene inhibits DNA synthesis in primary prostate epithelial cells in vitro and its administration is associated with a reduced prostate-specific antigen velocity in a phase II clinical study. *Prostate Cancer Prostatic Dis* 2006; **9**:407-413.
11. Brooks JD, Paton VG, Vidanes G. Potent induction of phase 2 enzymes in human prostate cells by sulforaphane. *Cancer Epidemiol Biomarkers Prev* 2001; **10**:949-954.
12. Singh AV, Xiao D, Lew KL, Dhir R, Singh SV. Sulforaphane induces caspase-mediated apoptosis in cultured PC-3 human prostate cancer cells and retards growth of PC-3 xenografts in vivo. *Carcinogenesis* 2004; **25**:83-90.
13. Saxe GA, Major JM, Nguyen JY, Freeman KM, Downs TM, Salem CE. Potential attenuation of disease progression in recurrent prostate cancer with plant-based diet and stress reduction. *Integr Cancer Ther* 2006; **5**:206-213.
14. Wilkinson S, Gomella LG, Smith JA, Brawer MK, Dawson NA, Wajsman Z, et al. Attitudes and use of complementary medicine in men with prostate cancer. *J Urol* 2002; **168**:2505-2509.
15. Chan JM, Elkin EP, Silva SJ, Broering JM, Latini DM, Carroll PR. Total and specific complementary and alternative medicine use in a large cohort of men with prostate cancer. *Urology* 2005; **66**:1223-1228.
16. Pierce JP, Natarajan L, Caan BJ, Parker BA, Greenberg ER, Flatt SW, et al. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on

prognosis following treatment for breast cancer: the Women's Healthy Eating and Living (WHEL) randomized trial. *JAMA* 2007; **298**:289-298.

17. Parsons JK, Newman V, Mohler JL, Pierce JP, Paskett E, Marshall J. The Men's Eating and Living (MEAL) Study: A Cancer and Leukemia Group B Pilot Trial of Dietary Intervention for the Treatment of Prostate Cancer. *Urology* 2008; in press.
18. Ornish D, Weidner G, Fair WR, Marlin R, Pettengill EB, Raisin CJ, et al. Intensive lifestyle changes may affect the progression of prostate cancer. *J Urol* 2005; **174**:1065-1069; discussion 1069-1070.
19. Bandura A. *Social foundations of thought and action: a social cognitive theory*. Prentice-Hall: Engelwood Cliffs, NJ, 1986.
20. Kahneman D, Tversky A (eds). *Choices, values, and frames*. Cambridge University Press: New York, 2000.
21. Bandura A. *Self-Efficacy: The Exercise of Self-Control*. W.H. Freeman and Company: New York, 1997.
22. Korfage IJ, Essink-Bot ML, Janssens AC, Schroder FH, de Koning HJ. Anxiety and depression after prostate cancer diagnosis and treatment: 5-year follow-up. *Br J Cancer* 2006; **94**:1093-1098.
23. Roth AJ, Rosenfeld B, Kornblith AB, Gibson C, Scher HI, Curley-Smart T, et all. The memorial anxiety scale for prostate cancer: validation of a new scale to measure anxiety in men with prostate cancer. *Cancer* 2003; **97**:2910-2918.
24. Dale W, Bilir P, Han M, Meltzer D. The role of anxiety in prostate carcinoma: a structured review of the literature. *Cancer* 2005; **104**:467-478.

25. Natarajan L, Flatt SW, Sun X, Gamst AC, Major JM, Rock CL, *et al.* Validity and systematic error in measuring carotenoid consumption with dietary self-report instruments. *Am J Epidemiol* 2006; **163**:770-778.
26. Muller H, Bub A, Watzl B, Rechkemmer G. Plasma concentrations of carotenoids in healthy volunteers after intervention with carotenoid-rich foods. *Eur J Nutr* 1999; **38**:35-44.
27. Lu QY, Hung JC, Heber D, Go VL, Reuter VE, Cordon-Cardo C, *et al.* Inverse associations between plasma lycopene and other carotenoids and prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2001; **10**:749-756.
28. Gann PH, Ma J, Giovannucci E, Willett W, Sacks FM, Hennekens CH, *et al.* Lower prostate cancer risk in men with elevated plasma lycopene levels: results of a prospective analysis. *Cancer Res* 1999; **59**:1225-1230.
29. Chen L, Stacewicz-Sapuntzakis M, Duncan C, Sharifi R, Ghosh L, van Breemen R, *et al.* Oxidative DNA damage in prostate cancer patients consuming tomato sauce-based entrees as a whole-food intervention. *J Natl Cancer Inst* 2001; **93**:1872-1879.
30. Campbell DR, Gross MD, Martini MC, Grandits GA, Slavin JL, Potter JD. Plasma carotenoids as biomarkers of vegetable and fruit intake. *Cancer Epidemiol Biomarkers Prev* 1994; **3**:493-500.
31. Giovannucci E, Rimm EB, Liu Y, Stampfer MJ, Willett WC. A prospective study of tomato products, lycopene, and prostate cancer risk. *J Natl Cancer Inst* 2002; **94**:391-398.

## **Figure Legend**

Figure 1. Flow diagram for patients treated with surgery or radiation in the Men's Eating and Living (MEAL) Study

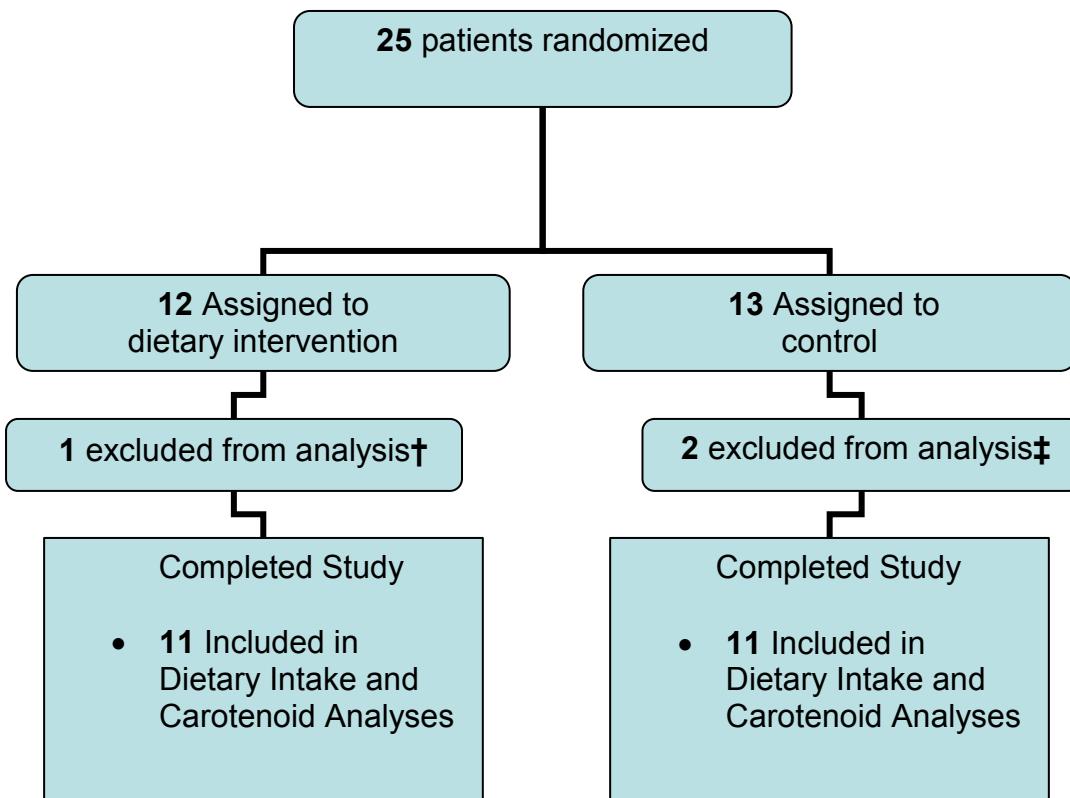
## **Table Legends**

Table 1. Prostate-specific antigen concentrations at baseline and 6 months among patients who had undergone surgery or radiation in the Men's Eating and Living (MEAL) Study.

Table 2. Vegetable intakes and nonvegetable mean intakes at baseline and 6 months assessed by using 24-hour dietary recall among patients who had undergone surgery or radiation in the Men's Eating and Living (MEAL) Study.

Table 3. Plasma carotenoid concentrations at baseline and 6 months among patients who had undergone surgery or radiation in the Men's Eating and Living (MEAL) Study.

**Figure 1**



† 1 lost to follow-up prior to 6-month data collection

‡ 2 lost to follow-up prior to 6-month data collection

**Table 1**

Primary therapy	PSA		
	Baseline	6-month	Group
Brachytherapy	2.43	1.74	Control
Brachytherapy	0.08	0.07	Control
Brachytherapy	0.66	1.06	Control
Prostatectomy	0.03	0.03	Control
Prostatectomy	0.03	0.03	Intervention
Prostatectomy	N/A	N/A	Control
Prostatectomy	0.03	0.03	Intervention
Prostatectomy	0.03	0.03	Intervention
Prostatectomy	0.48	0.55	Intervention
Prostatectomy	0.03	0.03	Control
Prostatectomy	0.03	0.03	Control
Prostatectomy	0.03	0.03	Intervention
Prostatectomy	0.03	0.03	Intervention
Prostatectomy	0.03	0.03	Intervention
Prostatectomy	0.03	0.03	Control
Prostatectomy	0.03	0.03	Control
Prostatectomy	0.12	0.14	Control
Prostatectomy	N/A	N/A	Intervention
Prostatectomy	0.03	0.03	Intervention
Prostatectomy	0.03	0.05	Intervention
Radiotherapy with androgen deprivation	N/A	N/A	Control
Radiotherapy with androgen deprivation	14.07	20.47	Intervention
Radiotherapy with androgen deprivation	0.33	0.41	Control
Radiotherapy with androgen deprivation	0.19	0.04	Intervention
Radiotherapy with androgen deprivation	0.25	0.13	Control

**Table 2**

	Intervention			Control		
	Baseline (n=12)	6 Months (n=11)	Change	Baseline (n=13)	6 Months (n=11)	Change
<b>Total vegetables<sup>1</sup></b>	3.3	5.6	70% <sup>2,3</sup>	4.0	3.5	-5%
<b>Cruciferous vegetables<sup>1</sup></b>	0.9	1.2	52% <sup>3</sup>	0.3	0.3	15%
<b>Tomatoes<sup>1</sup></b>	0.8	2.7	237% <sup>2,3</sup>	1.0	0.5	-22%
<b>Lettuce and potatoes<sup>1</sup></b>	0.6	0.3	-61%	0.6	1.0	40%
<b>Other vegetables<sup>1</sup></b>	1.9	2.6	45% <sup>2,3</sup>	2.4	2.1	-9%
<b>Fruit<sup>1</sup></b>	3.2	2.4	-31% <sup>3</sup>	2.8	1.8	-32%
<b>Whole Grain<sup>1</sup></b>	1.3	2.4	86% <sup>2,3</sup>	1.2	0.7	-48%
<b>Beans<sup>1</sup></b>	0.3	1.1	205% <sup>2,3</sup>	0.2	0.1	-32%
<b>Fiber (g/day)</b>	25.8	36.9	42% <sup>2</sup>	25.9	17.9	-31% <sup>3</sup>
<b>Fiber (g/1000 kcal)</b>	12.2	18.3	46% <sup>2,3</sup>	11.9	10.1	-9%
<b>Fat (% energy)</b>	33.2	26.4	-17% <sup>3</sup>	38.3	37.0	-2%

<sup>1</sup> Servings per day<sup>2</sup> Significant difference (p<0.05) between groups<sup>3</sup> Significant difference (p<0.05) within group

**Table 3**

Carotenoid (mmol/L)	Intervention (N=11)			Control (N=11)		
	Baseline	6 Months	Change	Baseline	6 Months	Change
<b>α-Carotene</b>	0.17	0.21	24%	0.16	0.16	-2%
<b>β-Carotene</b>	0.60	0.81	35%*	0.63	0.60	-4%
<b>Lutein</b>	0.49	0.55	12%	0.42	0.45	8%
<b>Lycopene</b>	0.83	0.93	12%	0.77	0.77	0
<b>Cryptoxanthin</b>	0.15	0.16	7%	0.15	0.18	23%
<b>Total Carotenoids</b>	2.25	2.66	19%*	2.13	2.17	2%

\* Significant difference ( $p<0.05$ ) within group